J. Pharm. Pharmacol. 1996, 48: 351–356
Received May 2, 1995
Accepted December 5, 1995

Effect of Activated Charcoal and Atropine on Absorption and/or Exsorption of Organophosphorus Compounds in Rats

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Abstract

Effects of activated charcoal and atropine for the removal of organophosphorus compounds, which remain in the gastrointestinal tract or have already been absorbed into the systemic circulation, were investigated in rats.

Activated charcoal extensively adsorbed the organophosphates fenitrothion, tolclofos methyl, piperophos and salithion, and its immediate administration after oral ingestion of fenitrothion remarkably reduced serum fenitrothion levels, but had no effect on the serum levels of the compound which had been absorbed from the gastrointestinal tract. Thus, all of the organophosphorus compounds were poorly exsorbed (0·002–0·39% of the dose in 120 min) from the blood into the intestinal lumen probably due to their extensive protein binding and large distribution volumes. Atropine inhibited absorption of fenitrothion in the perfusion in-situ and also delayed the absorption of the compound in-vivo, but had no significant effect on exsorption of fenitrothion. The serum fenitrothion levels on treatment with both atropine and charcoal significantly decreased compared with those of the control. We conclude that, oral activated charcoal will not be able to enhance the elimination of organophosphorus compounds which have already been absorbed into the systemic circulation, but constitute a useful method for the removal of the compounds remaining in the gastrointestinal tract because of its excellent adsorptive capacity.

Organophosphorus compounds such as fenitrothion, salithion and tolclofos methyl are widely used in agriculture as pesticides. Although the acute toxicities of these compounds are lower to mammals compared with those of earlier organophosphates such as parathion, the poisoning caused by accidental ingestion or attempted suicide is frequently fatal because of ingestion of the large doses. Acute poisoning by organophosphates results in accumulation of acetylcholine at end-plates, secondary to inhibition of acetylcholinesterase (AchE). The treatment of organophosphate poisoning is primarily performed with large doses of atropine, sometimes combined with the application of AchE reactivator such as pralidoxime (Taylor 1990). Atropine antagonizes the action of acetylcholine which is caused by the ingestion of organophosphates. However, atropine has no effect on nicotinic symptoms and central muscarinic effects and has little effect in blocking certain muscarinic effects. Pralidoxime is also effective only when the phosphorylated AchE has not undergone ageing and therefore should be administered as soon as possible to be available to newly-inhibited AchE (Lotti 1991). Thus, the treatment with these specific antagonists alone is insufficient for the patients poisoned by organophosphates. In acute organophosphate poisoning, complete and quick removal of the compounds is necessary before they are absorbed from the gastrointestinal tract. Procedures such as gastric lavage or induction of emesis with syrup of ipecac are generally followed and then administration of adsorbents such as activated charcoal with cathartics are applied (Lotti 1991).

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Several reports indicate that orally administered activated charcoal not only prevents drug absorption from the gastrointestinal tract but also increases clearance of drugs that have already been absorbed and are in the systemic circulation (Berlinger et al 1983; Mahutte et al 1983; Arimori et al 1989a). This so-called gastrointestinal dialysis (Levy 1982) has been noted as one of the haemo-purification methods in drug poisoning. We have confirmed that intravenously administered drugs are transferred into the small intestinal lumen to a significant extent in rats, and that the drugs can be removed by adsorption onto orally-administered activated charcoal (Arimori & Nakano 1985, 1986a, 1986b, 1987, 1988a). However, some reports have shown little effect on drug clearance following oral administration of activated charcoal possibly due to very large volumes of distribution (Goldberg et al 1985) or the extensive protein binding of drug (Arimori & Nakano 1988b). Accordingly, the usefulness of gastrointestinal dialysis is dominated by the extent to which the poisonous compounds are transported into the gastrointestinal tract. Thus, it is necessary to have information on the characteristics of transport of organophosphorus compounds from the blood into the gastrointestinal tract since whole bowel irrigation has generally been performed as a decontamination procedure in such poisoning. The whole bowel irrigation may not only clean the bowel, but also enhance the clearance of the toxic organophosphates if they are greatly exsorbed into the intestinal lumen.

The present work is aimed to elucidate the characteristics of exsorption of some organophosphorus compounds (fenitrothion, salithion and tolclofos methyl) and further to study whether multiple oral administration of activated

charcoal is a useful method for removing the toxic compounds in the systemic circulation as a haemopurification method.

Materials and Methods

Materials

Fenitrothion, tolclofos methyl and salithion were kindly supplied by Sumitomo Chemical Co. (Osaka, Japan), piperophos was from Takeda Chemical Industries (Osaka, Japan), and atropine sulphate from Tanabe Seiyaku Co. (Osaka, Japan). Activated charcoal was a product of Inuhinode Seiyaku Co. (Osaka, Japan) and particle size used in this study was less than 62 μm. All other chemicals used in this study were of analytical grade.

Adsorption study

In-vitro adsorption studies were carried out by dissolving fenitrothion, tolclofos methyl, salithion, cyanophos and piperophos in 50% ethanol solution. These organophosphorus compounds dissolved in various concentrations in the solutions (100 mL) were added to 10 mg activated charcoal in a series of conical flasks and the suspensions were shaken at 25°C. After equilibration, samples were filtered through a 0·45-μm pore-size membrane. Concentrations of each organophosphate in filtrate were determined, after suitable dilution, by spectrophotometry at 270 nm (fenitrothion), 220 nm (tolclofos methyl), 210 nm (salithion), 232 nm (cyanophos) and 210 nm (piperophos).

Estimation of adsorption parameters

Adsorption parameters were estimated according to the following Langmuir equation:

$$M = abC_{eq}/(1 + bC_{eq}) \quad (1)$$

where C_{eq} is the free drug concentration in solution at equilibrium; M is the amount of drug adsorbed by the quantity of charcoal used; a is the maximum amount adsorbed when the entire surface is covered by a monolayer and b is the equilibrium constant of the adsorption process.

Determination of partition coefficient and solubility

Both experiments were performed in a constant-temperature water bath (25·0 ± 0·1°C). Partition coefficient values were calculated based on the partition between *n*-octanol and distilled water. Both solvents were saturated with each other before starting the experiments. Organophosphorus compounds were dissolved in *n*-octanol at concentrations of 100 μg mL^{-1}. The solubility of each organophosphate was determined by adding the compound beyond its saturation point to distilled water and shaking the mixture for 5 h.

Examination of protein binding

Protein binding experiments were performed in triplicate by ultra-centrifugation using human serum. Briefly, serum aliquots (3 mL) were mixed with 20 μL organophosphates (1000 μg mL^{-1}) dissolved in methanol and incubated for 30 min at 37°C. After incubation, the samples were subjected to ultracentrifugation (220 000 *g*) for 18 h at 4°C.

Absorption and exsorption study

Male Wistar rats, 250–410 g, were fasted overnight with free access to water. The rats were anaesthetized by intraperitoneal injection of ethyl carbamate (urethane) at a dose of 1·2 g kg^{-1}. The small intestine was exposed by midline abdominal incision. The upper duodenum and the ileocaecal junction were cannulated with a polyethylene tube. Intestinal absorption and water transfer experiments were performed by a common in-situ recirculation perfusion method (Koizumi et al 1964). One hundred millilitres of lactated Ringer solution maintained at 37°C, containing fenitrothion (10 μg mL^{-1}) or ^3H_2O (0·74 MBq mL^{-1}) was perfused from the duodenum through the small intestine to the ileocaecal junction at a rate of 5 mL min^{-1}. Perfusates were collected at 0 and 60 min after starting the experiment. Intestinal exsorption experiments were performed using an in-situ single-pass perfusion technique (Arimori & Nakano 1985). Lactated Ringer solution (37°C) was perfused at 1·3 mL min^{-1} from the duodenum through the small intestine to the ileocaecal junction using a perfusion pump. Fenitrothion, tolclofos methyl and salithion were injected (7·5 mg kg^{-1}) into the left femoral vein. A 5-min perfusion period was allowed because of the lag phase of the equilibration period in all experiments. Atropine sulphate (2·5 mg kg^{-1}) was injected over about 1 min into the left femoral vein immediately and subsequently at 0·5 h intervals twice (absorption and water-transfer study) or four times (exsorption study) after the dose of fenitrothion.

Data analysis

The absorption rate constant (k_a) was obtained by using the following equation:

$$k_a = \ln(C_0 \cdot V_0/C_1 \cdot V_1)/t \quad (2)$$

where t is the perfusion time, C_0 and C_1 are the concentrations of fenitrothion in the perfusates at $t = 0$ and $t = 60$ min, respectively, and V_0 and V_1 are the volume of the perfusates at $t = 0$ and $t = 60$ min, respectively. The intestinal and biliary clearance values of organophosphates were calculated by dividing the amount of the compounds excreted in the perfusate and in the bile juice in 2 h by the area under the concentration–time curve (AUC) from 0 to 2 h, respectively.

In-vivo study

Male Wistar rats, 220–300 g, were fasted overnight with free access to water. Fenitrothion (100 mg kg^{-1}) was administered orally through a catheter. Activated charcoal suspended in water (150 mg mL^{-1}) was administerred orally at an initial dose of 300 mg immediately or at 1·5 h with additional doses of 150 mg three times at hourly intervals after the dose of fenitrothion. In the case of the control, water corresponding to the volume used for the charcoal suspension was given orally at each time. Blood samples (200 μL) were collected periodically from the tail vein. For the treatment with atropine, 2·5 mg kg^{-1} dose of the drug was administered intramuscularly at time zero, 0·5 and 1·5 h after the dose of fenitrothion.

Analytical method

Organophosphorus compounds in the serum, bile, urine and perfusate were analysed by gas chromatography-mass

spectrometry (GC-MS) using a glass column (1·0 m × 3 mm) packed with 3% OV-17 on Chromosorb WAW DMCS (60–80 mesh). Each sample (0·1–3 mL) was extracted with an adequate volume of *n*-hexane containing the internal standard (another organophosphate excluding the compound to be determined) after adding 0·1 mL (serum and bile) or 1 mL (perfusate) of 0·05 M sulphuric acid and then was centrifuged at 3000 rev min^{-1} for 10 min. The organic layer was separated into another tube and dried under reduced pressure at 35°C. The residue was redissolved in 30 μL *n*-hexane and a 1·0-μL volume of extract was injected directly into the GC-MS system. GC-MS was performed using a JEOL JMX-DX 303 mass spectrometer. The following GC conditions were used: helium gas flow rate 30 mL min^{-1}, inlet temperature 250°C, oven temperature 230°C, injection port temperature 250°C.

Pharmacokinetic analysis

The maximum serum concentration (C_{max}) and the time to achieve C_{max} (t_{max}) were obtained graphically. The areas under the serum concentration-time curve (AUC) of organophosphorus compounds were calculated by the trapezoidal rule. Intestinal and biliary clearance values of the organophosphates were calculated by dividing the overall amount of the compounds excreted into the perfusate or the bile in 2 h by the appropriate AUC values of the compounds obtained over the same period of time.

Statistical analysis

The unpaired *t*-test was used to assess the pharmacokinetic parameters. A probability level of $P < 0·05$ was considered significant.

Results

Adsorption of organophosphates onto activated charcoal

Since organophosphates are poorly soluble in water, adsorption isotherms of the four organophosphorus compounds onto activated charcoal were measured in 50% ethanol solution at 25°C. The adsorption parameters were estimated by fitting the data to the linearized form of Langmuir equation and are summarized in Table 1. It was shown that activated charcoal extensively adsorbed the organophosphorus compounds. The maximum adsorptive capacities (a) of activated charcoal for the organophosphates were 149–280 mg g^{-1} charcoal; the equilibrium constants (b) of activated charcoal were 0·104–0·147.

Table 1. Adsorption parameters onto activated charcoal and physicochemical properties of organophosphorus compounds at 25°C.

	Adsorption parameters[a]		PC[b]	Solubility (μg mL^{-1})
	[a](mg g^{-1})	[b](L g^{-1})		
Fenitrothion	280	0·121	19·4	41·3
Tolclofos methyl	249	0·147	8·51	3·91
Piperophos	175	0·111	9·54	64·8
Salithion	149	0·104	4·37	114

[a] Adsorption parameters were calculated according to Langmuir equation under the condition in 50% ethanol solution. [b] PC (partition coefficient) values were calculated based on the partition between *n*-octanol and distilled water.

Effect of atropine on fenitrothion absorption and water movement in-situ

The adsorption of fenitrothion from rat intestine was significantly reduced by the intravenous administration of atropine (5 mg kg^{-1}). The absorption rate constants (k_a) in the absence and presence of atropine were 0·053 ± 0·005 and 0·026 ± 0·004 min^{-1}, respectively ($P < 0·05$).

There was no significant difference in the water transport between treatments with and without atropine. Water movement from the intestinal lumen to the blood (absorption) tended to be more than that from the blood to the lumen (exsorption) irrespective of atropine dose (results not shown).

Exsorption of organophosphorus compounds

Fig. 1 shows the exsorption patterns of three kinds of organophosphorus compounds from the blood into the perfusate across the small intestinal mucosa following intravenous administration at each dose of 7·5 mg kg^{-1} to rats by the in-situ single-pass perfusion method. As shown in Fig. 1, the exsorption rate–time profiles reflected the serum level profiles. Fenitrothion, whose serum levels were highest of the three organophosphorus compounds, was also most extensively exsorbed into the perfusate. The average amounts of fenitrothion, salithion and tolclofos methyl

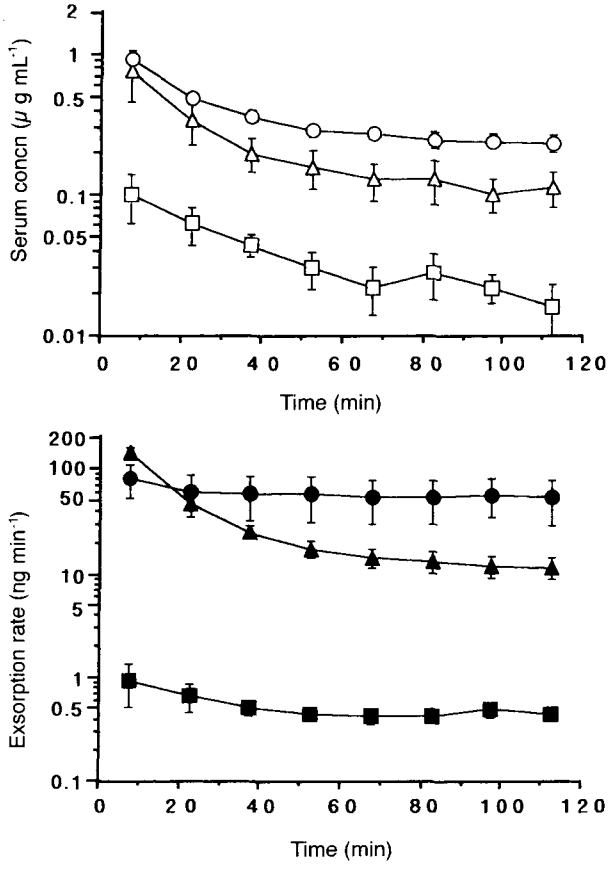

Fig. 1. The serum concentrations of organophosphorus compounds in the serum and their exsorption rates after intravenous administration at each dose of 7·5 mg kg^{-1} to rats. (○, ●) Fenitrothion; (△, ▲) salithion; (□, ■) tolclofos methyl. Each point represents the mean ± s.e. of 4–5 rats.

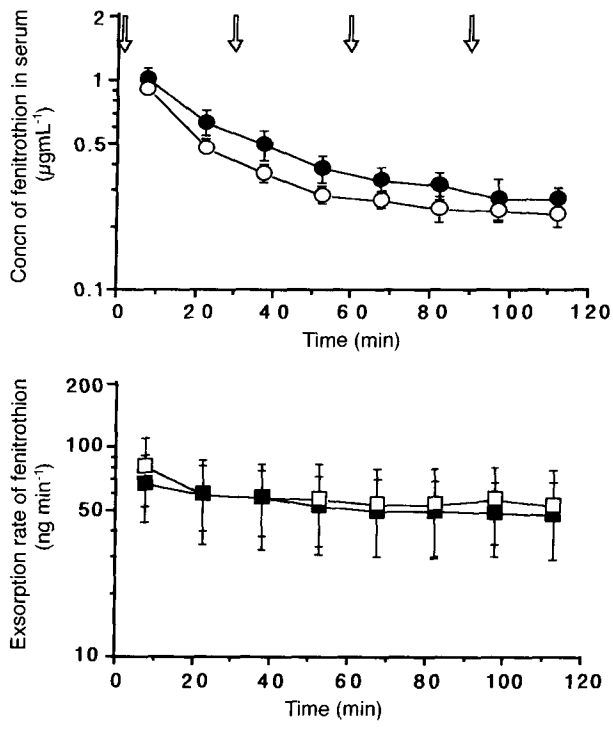

FIG. 2. Effect of atropine on the exsorption of fenitrothion after intravenous administration of fenitrothion at a dose of 7·5 mg kg^{-1} to rats. (○, □) Without treatment; (●, ■) treatment with atropine (0, 0·5, 1 and 1·5 h 2·5 mg kg^{-1} each). Each arrow indicates the time when atropine was administered. Each point represents the mean ± s.e. of 5 rats.

exsorbed into the perfusate were 0·39, 0·13 and 0·002% of the dose in 120 min, respectively. On the other hand, the amounts of fenitrothion, salithion and tolclofos methyl excreted into the bile were less than those into the perfusate and were 0·04, 0·01 and 0·002% of the dose in 120 min, respectively.

Effect of atropine on the exsorption of fenitrothion

The effect of atropine on the exsorption of fenitrothion was investigated in the same manner. Fig. 2 shows the exsorption patterns of fenitrothion from the blood into the perfusate across the small intestinal mucosa following intravenous administration at a dose of 7·5 mg kg^{-1} to rats in the presence or absence of atropine. There was no significant difference in the intestinal clearance values which were estimated from the amount excreted in the perfusate and the corresponding AUC (with atropine 7·53 mL h^{-1}, without atropine 9·97 mL h^{-1}).

Effect of activated charcoal and atropine on serum fenitrothion levels

Fig. 3 shows the time course of serum fenitrothion levels after oral administration of fenitrothion (100 mg kg^{-1}) to rats with or without oral activated charcoal from 0 to 3 h after the oral ingestion of fenitrothion significantly reduced serum fenitrothion levels compared with the corresponding control. On the other hand, oral administration of multiple doses of activated charcoal from 1·5 to 4·5 h had no significant effect on the serum fenitrothion levels. These results suggest that oral activated charcoal is available for

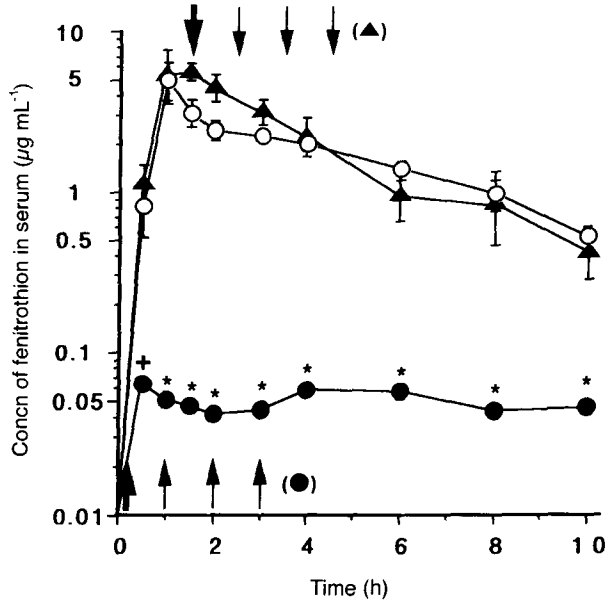

FIG. 3. The serum concentrations of fenitrothion after oral administration of fenitrothion at a dose of 100 mg kg^{-1} to rats with or without treatment with activated charcoal. (○) Without treatment; (▲) delayed treatment with charcoal (1·5 h: 300 mg, 2·5, 3·5 and 4·5 h: 150 mg each), (●) immediate treatment with charcoal (0 h: 300 mg, 1, 2 and 3 h: 150 mg). Each arrow indicates the time when activated charcoal was administered. Each point represents the mean ± s.e. of 6 rats. †$P < 0·05$, *$P < 0·01$ vs without treatment.

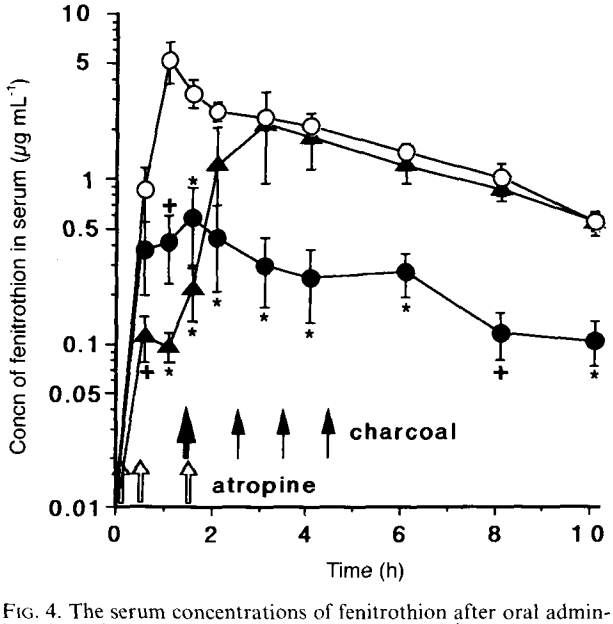

FIG. 4. The serum concentrations of fenitrothion after oral administration of fenitrothion at a dose of 100 mg kg^{-1} to rats with or without treatment with atropine and with combination of atropine and activated charcoal. (○) Without treatment; (▲) treatment with atropine (0, 0·5 and 1·5 h: 2·5 mg kg^{-1} each); (●) treatment with atropine (0, 0·5 and 1·5 h: 2·5 mg kg^{-1} each) and charcoal (1·5 h: 300 mg, 2·5, 3·5 and 4·5 h: 150 mg each). Each arrow indicates the time when atropine or activated charcoal was administered. Each point represents the mean ± s.e. of 6 rats. †$P < 0·05$, *$P < 0·01$ vs without treatment.

Table 2. Pharmacokinetic parameters of fenitrothion after oral administration (100 mg kg^{-1}) to rats with or without treatment with atropine or with combination of atropine and activated charcoal.

Parameters		Without treatment	With atropine	With atropine plus charcoal
AUC_{0-10h}	(μg h mL^{-1})	16·7 ± 1·09	9·63 ± 2·19[a]	2·49 ± 0·94[b]
C_{max}	(μg mL^{-1})	5·77 ± 1·10	1·84 ± 0·85[a]	0·67 ± 0·27[b]
t_{max}	(h)	1·25 ± 0·16	4·75 ± 0·65[a]	3·10 ± 1·07

Each value represents the mean ± s.e. of 6 rats. [a] $P < 0·05$, [b] $P < 0·01$ vs without treatment.

the removal of fenitrothion which has remained in the gastrointestinal tract but is not available for that which has been absorbed from the lumen and has been in the systemic circulation.

Fig. 4 also shows the time course of serum fenitrothion levels after oral administration of fenitrothion (100 mg kg^{-1}) to rats with or without treatment with atropine or atropine combined with oral activated charcoal. The serum levels of fenitrothion were significantly lower than those of the control during treatment with intramuscular atropine three times at a dose of 2·5 mg kg^{-1}, but gradually increased to the corresponding control levels with lapse of time. Atropine was administered at time 0, 0·5 and 1·5 h, thereafter and oral activated charcoal was administered 1·5, 2·5, 3·5 and 4·5 h after oral fenitrothion dose. As shown in Fig. 4, the serum fenitrothion levels after the treatment with both atropine and charcoal significantly decreased compared with those of the control. The pharmacokinetic parameters are shown in Table 2. The treatment with atropine significantly decreased the AUC and C_{max} values to about 58 and 32% compared with treatment with atropine alone, respectively, and both treatment with atropine and activated charcoal further decreased the values to about 15 and 12%.

Discussion

In acute organophosphate poisoning, the toxic substance should be removed as soon as possible before it is absorbed from the gastrointestinal tract. Since activated charcoal is able to adsorb a wide variety of drugs and toxins on its surface, it is generally used in combination with other decontamination procedures such as gastric lavage or whole bowel irrigation. As shown in Table 1, activated charcoal adsorbed fenitrothion, tolclofos methyl, piperophos and salithion to a great extent although presence of ethanol may reduce the adsorptive capacity of these organophosphates (Olkkola 1984). The adsorptive capacity of the organophosphorus compounds onto activated charcoal was relatively correlated with the apparent partition coefficient in the *n*-octanol system and was greatest for fenitrothion which has the highest lipophilicity. This may support the hypothesis that adsorption of chemicals onto charcoal is mainly mediated through a hydrophobic interaction (Nogami et al 1970; EL-Khordagui et al 1987).

In the present study, the organophosphorus compounds were poorly exsorbed in all cases from the blood into the intestinal lumen. Exsorption of compounds through the intestinal membrane could vary depending on physicochemical parameters such as the extent of binding to serum proteins, distribution volume and lipophilicity (Arimori & Nakano 1988b; 1989b). The extent of binding to serum proteins is an important factor in the permeation since it is well known that only the unbound compound can permeate through capillary walls to the gastrointestinal tract. The percentages bound to serum protein were more than 90% for all organophosphates (fenitrothion: 97·3 ● 0·24%, tolclofos methyl: 92·7 ± 4·77%, salithion: 96·9 ± 1·00%). Therefore, there are only small amounts of unbound fractions of the compounds available. Furthermore, these organophosphorus compounds are highly lipophilic as suggested from the large partition coefficient (Table 1) and thereby have large volumes of distribution. Accordingly, the poor exsorption of the organophosphates is considered to be due to their high degree of protein binding and large distribution volumes. There was a difference in the exsorption rates among the organophosphorus compounds. Although the amounts exsorbed into the intestinal lumen were small in all cases, the higher the serum levels of organophosphate, the greater exsorption is shown. Moreover, the exsorption rates were decreased with decrease in the serum levels. Consequently, these organophosphorus compounds seemed to be passively exsorbed according to the concentration gradients between the blood and the lumen.

Atropine is an important drug which antagonizes the excess actions of acetylcholine caused by organophosphate poisoning, but simultaneously inhibits the parasympathetic control of the gastrointestinal tract such as motility and gastric secretion. These actions have a great potential to affect the permeability of organophosphates. Atropine significantly inhibited the absorption of fenitrothion in the in-situ perfusion. A possible explanation for the decreased absorption of fenitrothion may be due to the decreased motility. The intestinal absorption of lipid soluble compounds is influenced by the unstirred water layer (Huang 1990). The flux of compounds across the unstirred water layer is inversely proportional to the thickness of this layer. Thus, atropine may increase the thickness of the unstirred water layer owing to the decrease in the intestinal motility. On the other hand, published studies have demonstrated that several lipid soluble compounds affect absorption or exsorption with a change in the transmucosal fluid movement by solvent drag (Ochsenfahrt & Winne 1974a, b). Atropine, however, had little effect on the absorption or exsorption of ^3H_2O across the intestinal membrane. This suggests that the decreased absorption of fenitrothion in the in-situ perfusion is not likely due to the inhibition of gastrointestinal fluid movement. Atropine had no effect either on exsorption of fenitrothion which was the most extensively exsorbed of the three organophosphates (Fig. 2). The lack of effect of atropine on the exsorption may be explained by the very small amount of the compound exsorbed across the intestinal membrane as described above. The sink condition between the blood and the intestinal lumen would have been kept in spite of change in the thickness of the unstirred water layer because of the poor exsorption. Accordingly, the thickness of unstirred water layer does not seem to be a limiting factor of the exsorption in this case.

Oral administration of activated charcoal had no effect on serum levels of fenitrothion which has been absorbed into the systemic circulation, but reduced the serum levels when charcoal was immediately administered after the ingestion of fenitrothion (Fig. 3). These results confirmed that activated charcoal could inhibit the absorption of fenitrothion remaining in the gastrointestinal tract if it is administered in the early stage of organophosphate poisoning.

Atropine is known to have a pronounced effect on gastric emptying and to reduce the rate of absorption of concomitantly administered drugs (Wing et al 1980; Rashid & Bateman 1990). Our in-vivo study also showed that intramuscularly administered atropine delayed absorption of fenitrothion (Fig. 4). Accordingly, the toxic organophosphates may have remained in the gastrointestinal tract by the delay of absorption in the case of patients treated with atropine. In such a case, oral administration of activated charcoal should be a useful method for the removal of organophosphates.

In conclusion, oral activated charcoal will not be able to enhance the elimination of organophosphorus compounds which have already been absorbed into the systemic circulation, but is a useful method for the removal of the compounds remaining in the gastrointestinal tract because of its excellent adsorptive capacity.

Acknowledgements

This work was supported in part by Grant-in-Aid for Scientific Research (No. 06672271) from the Ministry of Education, Science and Culture, in Japan.

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